

ANGULAR FORCES AROUND TRANSITION METALS IN BIOMOLECULES

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Abstract

Quantum-mechanical analysis based on an exact sum rule is used to extract an semiclassical angle-dependent energy function for transition metal ions in biomolecules. The angular dependence is simple but different from existing classical potentials. Comparison of predicted energies with a computer-generated database shows that the semiclassical energy function is remarkably accurate, and that its angular dependence is optimal.

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Biomolecular modeling with classical potentials has become an increasingly important tool in problems such as the determination of protein structure and function, and the design of new molecules with desired properties. With the continuing availability of increasingly powerful computers, one can only expect this growth to continue. A major roadblock toward expanded use of modeling with classical potentials is the absence of sufficiently reliable force laws for transition metals in biomolecules. The ability to treat transition metals is important because the active sites of many proteins are defined by transition metals; also smaller biologically active molecules often have transition metals as crucial constituents. In fact, transition metal complexes have been proposed as crucial ingredients in the origin of life itself [1]. Unlike the *s-p* constituents of biomolecules, which usually have unique, well-defined bonding configurations (such as *sp*² planar coordination), transition metals can adopt a broad range of asymmetric environments. This asymmetry is often important for the functioning of enzymes. Thus, for biomolecular modeling, one needs a “generic” potential which treats essentially all physically reasonable environments instead of perturbations relative to a single well-defined structure. *A priori*, one does not know the functional form of such a generic potential. The pair approximation, which ignores angular constraints, is applicable to simple metal ions, but not to transition metals. The transition-metal *d*-orbitals lead to complex angular forces which are manifested, for example, in the frequent occurrence of Cu²⁺ and Ni²⁺ ions in square-planar environments that are unexpected on the basis of pair interactions alone. In existing simulation codes based on classical potentials, the angular terms are usually either ignored [2–4], on the assumption that direct ligand-ligand interactions can take up most of the “slack”, or they are treated with simple assumed angular forms. The latter range from quadratic or higher order expansions about observed equilibrium bond angles [5–8] to more sophisticated expansions in trigonometric functions [9–12]. However, there has been no derivation of the angular form of classical potentials from quantum mechanics.

In this Letter, I use quantum-mechanical analysis to derive an energy function for *d*-electrons based on the local environment in biomolecules. The energy function has a “semi-classical” form, in the sense that it is slightly more complex than a classical additive sum of ligand-ligand interactions, but is still straightforward to treat in molecular modeling codes. To test the energy function, I generate a large number of random transition metal environments and evaluate their exact energies as a test set. The *d*-electron energy is described with surprising precision. The accuracy is much better than that of commonly used functional forms, and significantly improves on that of additive energy functions. The angular dependence of an energy function obtained by fitting to the exact energies is very similar to that derived analytically.

In biomolecules, transition metals are typically in a “coordination” bonding configuration. This differs from metallic bond in elemental transition metals in that the *d*-states usually hybridize with ligand orbitals at lower energies, rather than other *d*-orbitals at the same energy. This leads to well-defined discrete charge states. The physics of coordination bonding is well described by the ligand field theory [16] (LFT), which treats the *d*-shell in a transition-metal ligand complex by an effective *d-d* Hamiltonian:

$$\widehat{H}_d = \sum_{\mu,\nu} h_{\mu\nu} |d_\mu\rangle \langle d_\nu| \quad . \quad (1)$$

Here $|d_\mu\rangle$ and $|d_\nu\rangle$ are *d*-basis orbitals on the transition-metal ion, and the $h_{\mu\nu}$ contain the

effects of the ligands in a perturbative fashion:

$$h_{\mu\nu} = \sum_i \langle d_\mu | H | i \rangle \langle i | H | d_\nu \rangle / [E_d - E_i] \quad , \quad (2)$$

where the $|i\rangle$ are orbitals on the ligands that hybridize with the d -shell, and E_d and E_i are the d -shell and ligand-orbital energies, respectively. (The ligands are all taken to be equivalent for simplicity, but the more general cases are treated straightforwardly.) This approximate treatment describes the systematics of d -shell splittings in transition metal complexes quite well, although the electronic transition energies are not obtained quantitatively. In the case where only σ -type interactions between the ligands and the d -shell are present, the matrix elements of the effective Hamiltonian can be written [16] as

$$h_{\mu\nu} = \sum_i e(r_i) Y_\mu(\hat{r}_i) Y_\nu(\hat{r}_i). \quad (3)$$

where the Y_ν have the angular dependence of the d -basis orbitals, and the radial function $e(r_i)$ includes the effects of the energy denominator as well as the matrix elements.

The d -electron energy associated with \widehat{H}_d is obtained by simply adding the eigenenergies of the occupied d -states. This approximation is justified when comparing structural energies within a single well-defined charge/spin state. We focus on the “ligand-field stabilization energy” $E_{\text{LFSE}} = \sum_n \varepsilon_n - N_d \bar{\varepsilon}$. Here the first term denotes the eigenvalue sum, N_d is the number of d -electrons, and $\bar{\varepsilon}$ is the average energy of the d -complex (including both occupied and unoccupied states). As indicated in Fig. 1, splitting of the d -complex by ligand-field interactions provides a negative (stabilizing) contribution to E_{LFSE} if the d -shell is partly filled. The stabilizing contribution is enhanced if there is a gap between the highest occupied and lowest unoccupied states, as occurs for Cu^{2+} and Ni^{2+} ions in the square-planar coordination. We define the half-width W of the d -complex as the rms deviation of the energy eigenvalues from the d -complex average energy $\bar{\varepsilon}$. In the first approximation, one expects that E_{LFSE} should be proportional to W .

The d -electron energy function developed here gives E_{LFSE} as a simple function of the ligand positions. It is based on an exact sum rule that for W . Explicit calculation via Eqs. (1) and (2) shows that

$$5W^2 = \sum_n (\varepsilon_n - \bar{\varepsilon})^2 = \text{Tr}(\widehat{H}_d - \bar{\varepsilon} \hat{I})^2 = \sum_{i,j} U_{ij}, \quad (4)$$

where the ligand-ligand interaction is defined by

$$\begin{aligned} U_{ij} = & \left(\sum_\mu \langle i | H | d_\mu \rangle \langle d_\mu | H | j \rangle \right)^2 / (E_d - E_i)(E_d - E_j) \\ & - (1/5) \left[\sum_\mu \langle i | H | d_\mu \rangle \langle d_\mu | H | i \rangle / (E_d - E_i) \right] \\ & \times \left[\sum_\nu \langle j | H | d_\nu \rangle \langle d_\nu | H | j \rangle / (E_d - E_j) \right] \end{aligned} \quad (5)$$

For the case described by Eq. (3), the interaction takes the form

$$U_{ij} = e(r_i)e(r_j)[P_2(\cos \theta_{ij})^2 - (1/5)] \quad (6)$$

where $P_2(\theta) = (3 \cos^2 \theta - 1)/2$ is the second-order Legendre polynomial. This, and the assumption that E_{LFSE} is proportional to W , motivates the following choice for the functional form of E_{LFSE} in terms of the local environment:

$$E_{\text{LFSE}} = - \left[\sum_{ij} e(r_i)e(r_j)u(\theta_{ij}) \right]^{1/2} \quad (7)$$

where

$$u(\theta) = [P_2(\cos \theta_{ij})^2 - (1/5)]. \quad (8)$$

Because the square root of the ligand-ligand sum is taken, this type of energy function is different from classical additive angular interaction potentials. I call it a “semiclassical” energy function, since the steps in its calculation are similar to those in the calculation of a classical energy function, but quantum mechanical effects are included in a systematic fashion. It applies to one spin component of a transition metal d -shell; if both spin components contribute, then E_{LFSE} is simply the sum of contributions from the two components. The form (7) is parallel in form to “many-atom” [13] and “embedded-atom” [14] energy functions, but these are not angle-dependent. Modifications of the embedded atom method [15] have included angular dependence, but without quantum-mechanical grounding, assuming angular forms very different from the present ones.

In order to evaluate the accuracy of this functional form in the types of disordered local geometries that may be found in biomolecular environments, I have evaluated exact cluster energies (from the eigenvalues of Eq. (1)) for an ensemble of transition-metal complexes having random bond lengths and angles. The transition metal ions have six neighboring ligands. The coupling strengths $e_i = e(r_i)$ in Eqs. (3) and (7) vary randomly between 0 and 2 (in arbitrary units), corresponding to distances varying from a short-range cutoff to infinity, and the orientations \hat{r}_i are chosen at random. In this way, a very broad range of environments, with effectively varying coordination numbers, is sampled. Semiclassical energy functions of the form (7), as well as classical energy functions, have been least-squares fitted to the exact d -electron energies of these clusters, for the ions Fe^{2+} through Cu^{2+} , taken in the high-spin configuration (Mn^{2+} and Zn^{2+} are not included, since their minority-spin d -bands are empty and filled respectively, so E_{LFSE} vanishes). In the fits, in addition to the ligand-ligand interaction terms, we include a constant term in the ligand-ligand interaction, as well as a sum of single-ligand terms. Figure 2a shows the fit for Cu^{2+} obtained with the semiclassical energy function (7). The energies are fit remarkably well, with the standard deviation of 0.16 being less than 10 percent of the typical values of $|E_{\text{LFSE}}|$. Similar results are obtained for Ni. For Co^{2+} , the fractional error is about 15 percent. For Fe^{2+} , the magnitude of E_{LFSE} is found to be an order of magnitude smaller than for Cu^{2+} and Ni^{2+} , and the fractional error resulting from using the potentials is about 50 percent; nevertheless, the absolute errors are about half of those for Cu^{2+} and Ni^{2+} . Figure 2b shows corresponding results for a classical potential for Cu^{2+} of the form $\sqrt{e_i}\sqrt{e_j}\sin^2 2\theta$, where the angular dependence is taken from recent simulations of cluster energetics [12] and the $\sqrt{e_i}$ dependence follows from dimensional analysis and the linear scaling of E_{LFSE} with uniform

scaling the e_i . We take this form to be typical of the treatment of transition metals in standard modeling packages in which simple plausible forms are assumed. The fit is much less accurate, with a standard deviation of 0.49.

The energy function (7-8) provides an optimal description of the d -shell energetics in terms of two-ligand interaction interactions. To show this, I have fitted more elaborate potentials of the form (7) to the energy database, in which $u(\theta)$ is represented by a sum of terms of the form $\cos n\theta$, with $n \leq 8$. The results are shown in Fig. 3. The agreement between the optimized $u(\theta)$ and the form (8) is almost exact for Cu^{2+} and Ni^{2+} , and very good for Co^{2+} . For Fe^{2+} , the absolute discrepancies are small, but the relative discrepancies are larger. Note that the shapes of $u(\theta)$ as obtained here differ completely from the $\sin^2 2\theta$ form of Ref. [12], which is shown by the dotted curve in frame (a). In addition, I have tried modified forms of Eq. (7), in which the square root is replaced by a power law dependence, so that an exponent of unity gives an additive potential. The minimum error is obtained with an exponent very close to 0.50, corresponding to the Eq. (7). Thus we have fairly definitively pinned down the functional form of the angular forces around these ions. We note that these results are also applicable to the low-spin versions of the ions, by simple addition of contributions from the two subbands. Then, for example, low-spin Ni^{2+} becomes equivalent to high-spin Cu^{2+} .

The main chemical trend in $u(\theta)$ with changing d -count is a change in the magnitude of the potential, rather than its shape. The potentials for Ni^{2+} and Cu^{2+} are similar in magnitude, that for Co^{2+} roughly a factor of two weaker, and that for Fe^{2+} is weaker by an order of magnitude. The weakness of the Fe^{2+} potential can be partly understood by analysis of the energetics of four-ligand complexes. For these, \widehat{H}_d , as given in Eq. (1), is a sum of four one-dimensional projection operators thus has rank four. One readily shows that all of its eigenvalues are nonnegative. This means that the lowest eigenvalue is zero, independent of the angular arrangement of the ligands. In the case of Fe^{2+} , there is only one d -electron, which resides in the orbital having the zero eigenvalue. Thus there are no angular interactions for Fe^{2+} with four ligands. For cases with higher coordination, the lowest eigenvalue will still likely be close to zero unless the five contributing projection operators are orthogonal to each other. From the point of view of practical application, the variations seen in Fig. 3 suggest that the inclusion of angular forces for modeling Cu^{2+} and Ni^{2+} is crucial, but that the Fe^{2+} ion (in high-spin configuration) might well be modeled with only radial interactions.

These features can be used to explain the observed chemical trends in the relative stability of square and tetrahedral structures in these systems. I have evaluated the energy difference ΔE between E_{LFSE} between the square and tetrahedral coordination geometries. Comparisons between the exact values and those obtained by Eq. (7) and the empirical potential [12] are shown in Fig. 4, for the transition metal ions Fe^{2+} through Cu^{2+} . The empirical-potential results are much too small, but the basic trends of the exact results are also seen in the semiclassical results, with the square structure favored strongly for Ni^{2+} and Cu^{2+} . This trend is consistent with known structures of four-ligand transition metal complexes. Such complexes of Ni^{2+} and Cu^{2+} overwhelmingly adopt square coordination, in the absence of steric constraints, while Fe^{2+} and Co^{2+} generally have tetrahedral coordination [17,18]. (We note that the experiments do not necessarily establish the sign of the electronic contribution ΔE calculated here for a given system, since direct electrostatic

interactions between the ligands tend to favor tetrahedral coordination; only the trend with varying d -count is established.) The structural energies can be understood with the help of the potentials shown in Fig. 3. The minima at 0° and 180° favor the square structure in all cases, but are weaker for Fe^{2+} and Co^{2+} . In fact, the calculated values of ΔE correspond fairly closely to the strengths of the angular interactions. The energy differences are not, however, obtained quantitatively by the semiclassical energy function. The discrepancy lies mainly in the energy of the tetrahedral structure. For tetrahedral Co^{2+} , for example, the semiclassical energy function underestimates $|E_{\text{LFSE}}|$ by about 20 percent.

In summary, I have shown that a new semiclassical angular energy function, with a simple analytic angular dependence, describes the ligand-field stabilization energy for transition-metal ions in biomolecules remarkably well. The theoretical form for the angular dependence is strongly confirmed by analysis of a large computer-generated database of complexes. Analysis of the angular form of the interactions justifies the systematics of the relative stability of square and tetrahedral packing in terms of the behavior of the interactions at 0° and 180° . Incorporation of this form of energy function into existing biomolecular simulation packages should significantly enhance their reliability, and lead to new possibilities for design of metal-containing biomolecules.

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FIGURES

FIG. 1. Ligand-field splitting of Ni^{2+} d -shell in square coordination. Only minority spin band, in high-spin configuration, is shown.

FIG. 2. Accuracy test of semiclassical and empirical energy functions, in comparison with exact quantum-mechanical results for ligand-field Hamiltonian. Energy unit is average coupling of single ligand to transition-metal d -shell.

FIG. 3. Angular dependence of energy function. Solid lines: ten-parameter fit to exact energies. Dashed lines: derived angular function from Eq. (8). Function $u(\theta)$ is dimensionless. Frame (a) Cu^{2+} ; (b) Ni^{2+} ; (c) Co^{2+} ; (d) Fe^{2+} . Dotted line in frame (a) is empirical energy function from Ref. [12], with magnitude adjusted for clear comparison.

FIG. 4. Energy differences ΔE between square and tetrahedrally coordinated transition metal ions. Energy unit is coupling strength between single ligand and transition metal. Solid circles: exact treatment of ligand-field Hamiltonian. Open circles: semiclassical energy function (Eq. (7)). Triangles: empirical energy function (Ref. [12]).







